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BRIEF REPORT

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Primary effusion lymphoma in human immune deficiency (HIV)-negative non-organ transplant immunocompetent patients

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Abstract

Primary effusion lymphoma (PEL) is a rare non-Hodgkin's lymphoma most commonly occurring in the context of human immune deficiency (HIV) infection. Herpes virus 8 (HHV-8) has been associated with PEL and considered to be the etiologic agent. In addition, most cases (60%-90%) also show evidence of Epstein-Barr virus (EBV) infection. We describe here an elderly man who was HIV seronegative and immunocompetent, and presented with worsening weakness and ascites. The diagnosis of PEL was rendered cytologically and supported by the results of flow cytometry. The presence of HHV-8 was demonstrated by immunohistochemistry, whereas EBV-associated genetic material was absent by EBER ISH. No lymphadenopathy or organ involvement with lymphoma was found. Systemic chemotherapy with lenalidomide was started given the poor prognosis and commodities of severe coronary artery disease; however, the patient did not respond and succumbed to his disease in 4 months. We present detailed cytologic and clinical findings of this very rare occurrence, and review literature of all reported PEL cases of HIV-negative, nontransplant, immunocompetent patients.

KEYWORDS

HIV-negative, immunocompetent, non-organ transplant recipient, primary effusion lymphoma

1 | INTRODUCTION

Primary effusion lymphoma (PEL) is a rare non-Hodgkin's lymphoma, usually occurring in the context of human immune deficiency (HIV) infection or affecting patients who are often elderly or immunocompromised. It commonly presents as malignant effusions in body cavities such as the pleural space, pericardium, and peritoneum. PEL was first described in 1989,[1] and since then, our understanding of its unique pathogenesis has expanded, specifically its association with human herpesvirus-8 (HHV-8) infection.[2] It is generally considered an aggressive lymphoma; the prognosis is poor with a mean overall survival of 6 months even with combination chemotherapy.[3] We describe herein the detailed cytomorphologic and immunohistochemical features of a unique case of PEL from an immunocompetent HIV-negative patient, and compare it to other similar reported cases in the literature. We also summarized the clinico-demographic features and outcomes of currently published HIV-negative PEL cases in non-post-transplant, immunocompetent patients.

2 | CASE PRESENTATION

A 72-year-old Caucasian male with a past medical history significant for coronary artery disease, status post coronary artery bypass grafting surgery, presented with 6 months of worsening weakness and abdominal swelling. He was active and relatively well until the

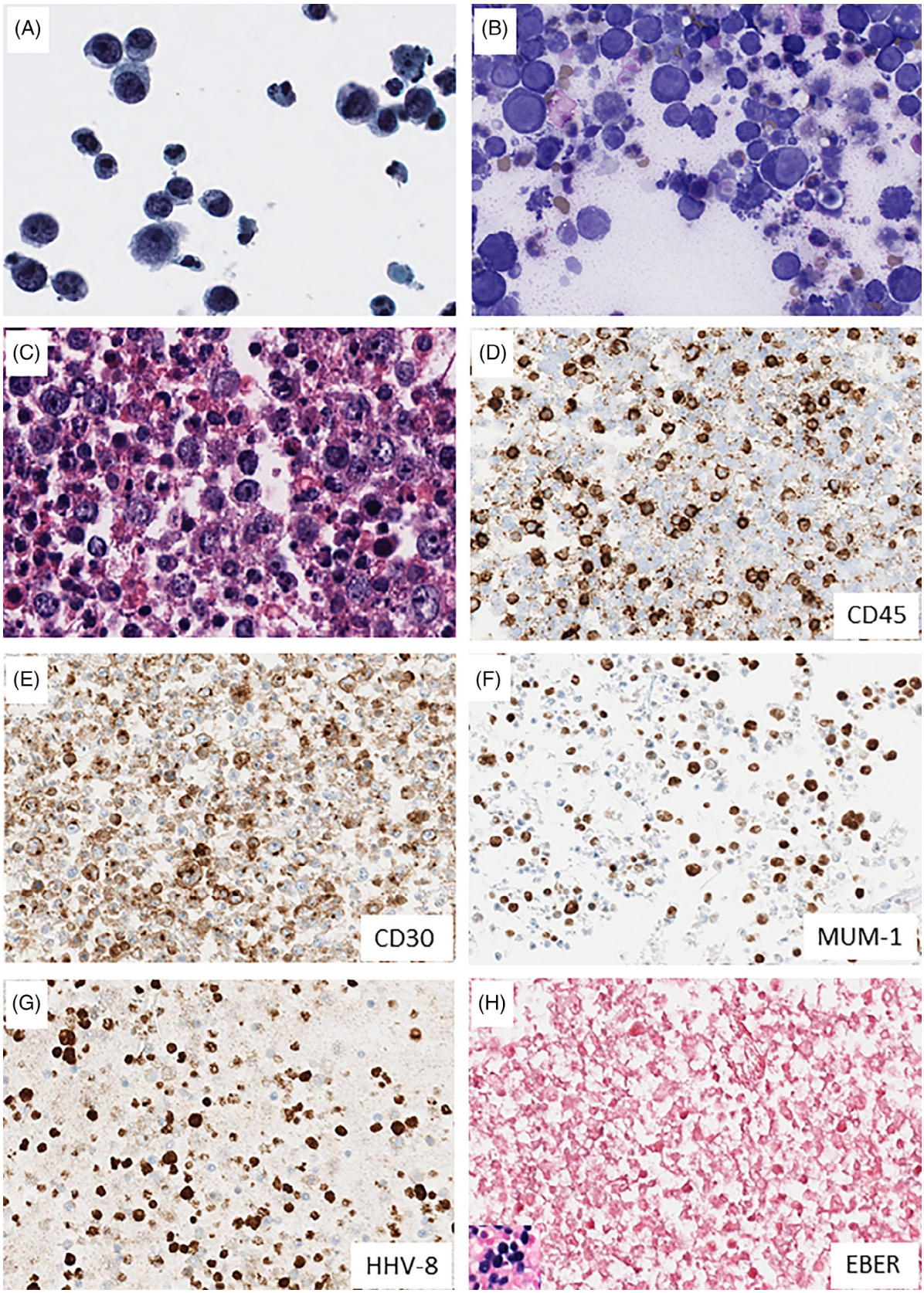

FIGURE 1 Morphology and immunophenotype of primary effusion lymphoma (PEL). Ascites fluid shows pleomorphic large cells with irregular nuclear contours, prominent nucleoli, and moderately abundant cytoplasm (A, Papanicolaou, ×400) (B, Diff-Quick, ×400) (C, H&E, ×400). (D-G) Neoplastic cells were negative for B- and T-cell markers (data not shown), but were positive for CD45, CD30, MUM-1, and HHV8 human herpesvirus-8 (×200). (H) Neoplastic cells were negative for EBER-CISH (×200, inset showing the RNA internal control) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Differential diagnosis of primary effusion lymphoma (PEL)

		IHC							ISH
	Association with ID	Epithelial markers	Melanocytic markers	T-cell markers	B-cell markers	Plasma cell markers	CD30	HHV-8	EBER
Metastatic carcinoma	N/A	Pos	Neg	No	No	N/A	N/A	N/A	N/A
Melanoma	N/A	Neg	Pos	No	No	N/A	N/A	N/A	N/A
Hematopoietic malignancies									
Plasmablastic lymphoma	Yes	No	No	Neg	Weak or absent	Pos	Neg	Neg	Pos[a]
Anaplastic large cell lymphoma	No	No	No	T- or null-cell lineage	Neg	Neg	Pos	Neg	Neg
Pyothorax-associated lymphoma	No	No	No	Neg	Pos (nongerminal center)	MUM1 (+), CD138 (±)	Neg	Neg	Pos[b]
Burkitt lymphoma	Yes	No	No	Neg	Pos (germinal center)	Neg	Neg	Neg	Pos[c]
Primary effusion lymphoma	Yes	No	No	Aberrant expression	Neg	Pos	(±)	Pos	Mostly Pos

Abbreviations: EBV, Epstein-Barr virus; HHV-8, human herpesvirus-8; ID, immunodeficiency; N/A, not applicable; Neg, negative; Pos, positive.
[a]About 70% of plasmablastic lymphoma cases express EBV-encoded RNA (EBER).[12]
[b]In situ hybridization study showed that pyothorax-associated lymphoma in 70% of the patients was Epstein-Barr virus (EBV)-positive.[13]
[c]Positive in endemic, rarely positive in sporadic, and 30% of AIDS-associated Burkitt lymphoma are EBV-positive.[14]

current illness. He was found to have a large amount of ascites on abdominal ultrasound and congestive hepatopathy. He subsequently underwent paracentesis, and the ascites fluid was sent to the laboratory for body fluid analysis and cytology.

On cytology, the peritoneal fluid showed a malignant large cell population, associated with abundant apoptosis and mitosis (Figure 1A-C). The neoplastic cells showed positive staining with CD45, CD30, MUM1, and HHV8 (Figure 1D-G). There was negative staining with AE1/AE3, Cam 5.2, HMB45, CD3, CD20, PAX5, ALK1, and CD138. Kappa and Lambda immunohistochemical stains showed only nonspecific staining. Flow cytometry showed large lymphoid cells that were positive for CD2, CD79b, and CD45 (dim), while they were negative for CD3, CD5, CD10, CD19, and CD20, and did not express surface immunoglobulin light chains. This immunoprofile confirmed the lymphoid nature of the malignant cells, and excluded an epithelial or melanocytic malignancy. In addition, the lymphoma cells lacked many B-cell and T-cell antigens and were HHV8-positive, consistent with PEL. EBER CISH for EBV was negative (Figure 1H).

Given the poor prognosis of PEL and comorbidities of the patient, he was not felt to be a candidate for cytotoxic chemotherapy. HIV serologies were negative; therefore, no antiretroviral therapy regimen was given. The patient was started on lenalidomide, but unfortunately, he did not respond to the therapy and died 4 months following the diagnosis of PEL.

3 | DISCUSSION

The diagnosis of PEL is characteristically made on a cytological examination of the involved effusion fluid, since nodal and organ involvement is usually absent. Kaposi's sarcoma-associated herpes virus (HHV-8) is attributed to be the etiologic agent in PEL, therefore, a definitive diagnosis of PEL relies on the detection of HHV-8 infection in the malignant cells. HHV8 was first characterized in HIV-infected patients with Kaposi's sarcoma in 1994.[4] Subsequently, HHV-8 was found to be associated with other disorders, including PEL[2] and a form of multicentric Castleman disease.[5] It is a linear double-stranded DNA virus, a member of the gamma herpes virus family which also includes EBV. HHV-8 is endemic in sub-Saharan Africa (50%-70% seroprevalence) and the Mediterranean region (20%-30% seroprevalence), while a low 1% to 3% infection rate is found in asymptomatic blood donors in North America.[6] Most cases (60%-90%) of PEL also show evidence of Epstein-Barr virus (EBV) infection, and can be demonstrated by in situ hybridization for EBV-encoded small RNA.[7]

PEL is clinically characterized by malignant effusions in body cavities, usually without associated extracavitary tumor masses. Symptoms are usually a result of mass effects from the accumulation of the serous effusion, as a result, patients commonly present with dyspnea or abdominal distension. Dissemination to distant sites is not uncommon and most patients have a short survival of several months after initial diagnosis.[8] The most frequent causes of death are opportunistic infection, HIV-related complications, and progression of lymphoma.[9]

Cytologic evaluation reveals large malignant cells with round to irregular nuclei, prominent nucleoli, and varying amounts of deeply basophilic cytoplasm, that is, occasionally vacuolated. The cells range in appearance from immunoblastic to plasmablastic to anaplastic. High mitotic and apoptotic rates are frequently observed.[10] PEL cells express CD45, but usually display a null lymphocyte phenotype with negative T-cell (CD3, CD4, and CD8) markers and B-cell (CD19, CD20, and CD79a) makers by immunohistochemistry. Molecular

TABLE 2 Clinico-demographic features and outcome of HHV-8 (+), HIV (–) patients who are not transplant recipients, and not immunocompromised

Case	Age (years)	Gender	Initial sites	Clinical history	Treatment	Survival (months)	Ethnic origin
1[18]	85	F	Pleura	KS of both legs	Unknown	4	Russian
2[19]	94	M	Peritoneum	KS of the right foot	Drainage	3	Unknown
3[20]	85	M	Pleura	None significant	CHOP	2	Unknown
4[21]	75	M	Pleura	COPD, dilated cardiomyopathy	None	≥12	Italian
5[22]	83	M	Pleura	Ischemic myocardiopathy	None	0.1	Spanish
6[23]	73	F	Peritoneum	Concurrent MCD and KS	CHOP X 4	4	Jewish of Ashkenazi origin
7[24]	68	M	Pleura and Peritoneum	CABG	CHOP X 4	9	Jewish of Moroccan origin
8[25]	80	M	Pleura	Ischemic heart disease, COPD	CHOP X 4	≥8	Unknown
9[17]	78	M	Pleura	CVA, tuberculosis	CHOP	18	Jewish of Eastern European origin
10[26]	92	M	Pleura, peritoneum	KS	Etoposide and prednisone	3	Mediterranean
11[27]	78	M	Peritoneum	CHF	C, P	1.5	French origin
12[27]	86	F	Peritoneum	Cutaneous KS, MCD, disseminated varicella, remote history of breast cancer s/p surgery and radiation 20 years ago	CHOP	2	French origin
13[28]	74	M	Pleura	Ischemic heart disease	Unknown	Unknown	Ashkenazi Jewish
14[29]	78	M	Pleura and pericardium	Fluctuating anemia and mild lymphadenopathy with normal bone marrow biopsy	CHOP X2/Cidofovir-radiotherapy	≥15	Italian heritage
15[30]	78	M	Pleura	CAD, stroke, CHF	Bortezomib, doxorubicin, rituximab	≥24	Mediterranean origin
16[31]	66	M	Peritoneum	HCV	None	≥6	Unknown
17[31]	86	M	Pleura, peritoneum	Asbestos exposure	None	1	Unknown
18[32]	87	F	Pleura	Heart failure	Pleurodesis	29	Portuguese
19[33]	73	M	Pleura	Progressive gastric cancer	R-THP-COPX2	≥11	Japanese
20[34]	86	M	Pleura	ESRD on hemodialysis	Supportive	7	Japanese
21[35]	77	M	Peritoneum	CAD, CHF, and intracerebral hemorrhage	Lenalidomide	≥18	Lebanese
22[36]	70	M	Pleura	Remote history of lung cancer	CHOP	≥11	Korean
23[36]	67	M	Pleura	HBV	CHOP	≥9	Korean
24[36]	78	F	Pleura	None significant	None	49	Korean
25[36]	87	M	Pleura	None significant	None	≥6	Korean
26[36]	60	M	Pleura, pericardium, peritoneum	None significant	CHOP	≥173	Korean
27[37]	60	F	Pleura, pericardium, peritoneum	None significant	COP	≥24	Hispanic
28 (current case)	72	M	Peritoneum	CAD, s/p CABG	Lenalidomide	4	Caucasian, Hispanic

Abbreviations: AAA, abdominal aortic aneurysm; CABG, coronary artery bypass grafting surgery; CAD, coronary artery disease; CHF, congestive heart failure; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; COP, cyclophosphamide, vincristine, and prednisolone; COPD, chronic obstructive pulmonary disease; C, P: cyclophosphamide, prednisolone; CVA, cerebrovascular accident; ERSD, end-stage renal disease; DM, type 2 diabetes; HBV, hepatitis B virus; KS, Kaposi's sarcoma; MCD, multicentric Castleman's disease; R-THP-COP, rituximab, pirarubicin, cyclophosphamide, vincristine, and prednisolone; s/p, status post.

studies have provided evidence that the PEL cell of origin is closely related to postgerminal center B-cells and likely of plasmablastic derivation.[11]

Differential diagnostic consideration in PEL includes metastatic carcinoma, malignant melanoma, and other hematopoietic malignancies, such as plasmablastic lymphoma, anaplastic large cell lymphoma (ALCL), pyothorax-associated lymphoma, and Burkitt lymphoma. Immunohistochemistry, ISH, and flow cytometry, in addition to clinical features, are needed to make a definitive diagnosis (see Table 1). Epithelial markers such as cytokeratins, Moc 31, and Ber-EP4 should be performed to exclude metastatic carcinoma, while melanocytic markers such as HMB45, melanin A, and SOX10 help exclude melanoma. PEL cells are positive for HHV-8 while negative for T- or B-cell markers. In contrast, other hematopoietic malignancies in the differential are negative for HHV-8. Pyothorax-associated lymphoma and Burkitt lymphoma express B-cell markers and are often positive for EBV[13,14]; plasmablastic lymphoma express plasma cell markers and the majority of such cases are EBV positive[12]; ALCL may express T-cell markers and are strongly positive for CD30 and also ALK in a subset of ALK-positive ALCL. In addition, PEL cells stain negatively for keratin and melanocytic markers to aid in the differential diagnosis of metastatic carcinoma or melanoma.

PEL has been uncommonly described in HIV-negative patients who are immunocompromised, including those who are solid organ transplantation recipients, postchemotherapy, or patients with cirrhosis and/or diabetes mellitus.[15-17] In rare instances, elderly immunocompetent patients who lived in geographic areas with high HHV8 prevalence, such as the Mediterranean region, have been diagnosed with PEL that showed evidence of HHV-8 infection without EBV.[17]

The patient described in our case report was immunocompetent, originally from Central America (Hispanic), and had no links to parts of the world where HHV8 is endemic. Table 2 summarizes the clinicodemographic features and outcomes of HIV-negative immunocompetent PEL cases published to date. Only 27 other cases with clinical and virological features similar to those of our patient (HIV-negative, HHV-8 positive), who are not organ transplant recipient and not immunocompromised have been reported in the literature. The majority of these patients are males in their 70s, with at least 32% of these patients being of Mediterranean origin. Notably, 18% of these patients had a prior history of Kaposi's sarcoma; while 7% had history of cancer without known chemotherapy.

The average overall survival of PEL in this patient population is 17 months, with a bimodal distribution. There is no standard treatment, but 50% of patients received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or modified CHOP chemotherapy. There was a slight survival advantage between patients who received chemotherapy (n = 17, 22 months) and those who received pleurodesis, thoracentesis, or supportive care only (n = 9, 13.8 months); however, no statistical significance was achieved. The molecular drivers for PEL are still unknown; nonetheless, emerging therapies such as targeted therapy for activating pathways in PEL such as mammalian target of rapamycin (mTOR) are being investigated,[38] immunomodulatory drugs such as lenalidomide are in clinical trial.[39]

In summary, we here presented a very rare case of PEL from an immunocompetent, HIV-negative patient, and reviewed the literature, with only 27 similar cases have been previously reported. It is important to recognize that although the majority of PEL patients are immunocompromised, complete pathologic workup is still necessary to rule out PEL in immunocompetent patients presenting with a malignant effusion cytology.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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